Applicants have anatomized the *Wands* factors previously and incorporate same again herein.[1] Notwithstanding, the Advisory Action alleges that the silence of the prior art taken with purported lack of extrapolatable structural features for "any compound" evincing the subject selectivity accords to deficient enablement. The official parting shot is that to "make and test" compounds for the selectivity aforesaid is not the standard under 112.

Applicants disagree.

First, contrary to the Official Action, the claims are not directed to "any compound" having said selectivity: they are expressly and unequivocally directed to "a hydroxamic acid compound." The reader thus knows exactly which class of compounds to consider. Moreover, the reader is given examples (non-limiting) of such compounds, both in the guise of a Formula I genus, and then from the various specific embodiments. This guidance is directive as to hyroxamic acids suitable for the present invention. That not every possible hydroxamic acid manifesting the requisite behavior may be encyclopedically delineated *pro arguendo* is of no moment inasmuch as an applicant is not required to so exhaustively and definitively list. Indeed, the Official Action concedes enablement for certain compounds, but takes the position that any need on the reader's part to undertake some effort to identify compounds (again: hydroxamic acids) beyond this forecloses enablement.

This is not the case in fact or law: factually, the specification provides clear cut directions on the type of assays to be used for such assessment: for TNF- α selectivity, human monocyte assay; for MMP-1, *in vitro*.

Legally, making and testing (experimentation) is quite permissible under 112. Indeed, a sizeable amount of experimentation is perfectly acceptable, if routine. The prohibition is not to the amount of experimentation, but to the undueness of it: if it veers from the ordinary to the extraordinary then and only then are 112, 1st ¶ issues raised. See e.g. *PPG Indus. Inc. v. Guardian Indus. Corp.* 37 USPQ2d 1618, 1623 (Fed Cir 1996):

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed...."

Insofar as Claims 61 and 81 are concerned, the specification provides clear guidance as to the nature of the compound and the direction of experimentation, to the extent needed:

[1] See e.g. Amendment After Final Rejection, October 16, 2002.

hydroxamic acids; as represented by the genus of formula I and further by e.g. the species exemplified;[2] the type of assays for TNF-α selectivity, and MMP-1, respectively.

This satisfies 112. Such conclusion is moreover independently, objectively and factually corroborated. Specifically, a plethora of publications employing the techniques disclosed in the specification to determine the very selectivity questioned by the Examiner exist which substantiate the adequacy of the subject disclosure. Attention in this regard is directed to the attached articles --namely:

- Letavic et al., Bioorg. Med. Chem. Lett. (2002), 12, 1387
- Levin et al., Bioorg. Med. Chem. Lett. (2001), 11, 2189
- Duan et al., J. Med. Chem. (2002), 45, 4954

Among other things, these references establish that others have used the very observations described in the present application to prepare a variety of TACE inhibitors with selectivity over MMP-1, including hydroxamic acid compounds having a variety of substituents representatively disclosed by Formula I.

Thus for example: Letavic et al. discloses >100X selectivity for TACE over MMP-1 with hydroxamic acid compounds having various benzyloxyaryl and like substituents as claimed. Similarly, Levin et al. report on anthranilic hydroxamate inhibitors of TACE wherein various hydroxamic acids with assorted benyloxyaryl or heteroarylmethoxyaryl substituents have >100X selectivity for inhibition of TACE over MMP-1. Duan et al. discuss α-lactam hydroxamate inhibitors of TACE having various benzyloxyaryl or heteroarylmethoxyaryl substituents and >100X selectivity of TACE over MMP-1.

Applicants have provided new claims 82 and 83 directed to embodiments of the invention wherein the hydroxamic acid compound comprises a $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, $(C_6\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_{10})$heteroaryl, $(C_1\text{-}C_{10})$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, or $(C_1\text{-}C_{10})$heteroaryl$(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_{10})$heteroaryl group consistent with the foregoing. Applicants' inclusion of said new claims is without prejudice to existing claims and examination/patentability of same, including under 112.

Further evidence of how the subject methodology has been successfully employed by others –and hence proving sufficiency of description herein-- to produce inhibitors with, e.g. various Q groups as recited in the embodiment of Claim 1 include:

[2] In this regard, the official opinion has been that Table A shows more compounds failing to show the selectivity, than do. This is not understood. Table A specifically lists TACE/MMP-1 ratios falling within the range(s) claimed.

WO 03016248
US 6225311B1
US 6197791B1
US 6172057B1
WO 0044709A2
WO 9958531A1
WO 9942436A1
US 5929097
WO 9838163A1
WO 9837877A1
WO 9816503A2
WO 9506031A1
WO 0292588A2
WO 0274738A2
WO 0255516A2
WO 0255491A2
US 6376506B1
US 6358980B1
WO 0204416A2
WO 0170734A2
WO 0170673A2
WO 0160808A1
US 6225311B1
US 6197791B1
US 6172057B1
WO 0063197A1
WO 0059874A1
WO 0059285A2
US 6114367
WO 0044723A1
WO 0044709A2
WO 0040576A2
WO 9958531A1
US 5952320A
WO 9942436A1
WO 9940063A1
US 5883131
US 5817822
WO 9838163A1
WO 9837877A1
WO 9834918A1
WO 9832734A1
WO 9816503A2
WO 9814424A1
WO 9807697A1
EP 818442A2
WO 9805635A1
WO 9743249A1
WO 9724117A1
WO 9524398A1
WO 9506031A1

Assuming that copies of the foregoing are conveniently available to the Examiner, same have not been included herewith. If however, this is not the case, the Examiner may contact the undersigned at the telephone number indicated upon which copies will be promptly dispatched.

Accordingly, it is submitted that the pending claims –61, 81 and 82—are patentable and meet the strictures of 35 USC 112 in all respects. Withdrawal of the instant rejection is solicited.

WHEREFORE in view of the above, allowance of the instant case is earnestly requested.

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Richard L. Catania
Reg. No. 32,608
Attorney for Applicants

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(212) 733-6513